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INHALABLE POWDER CONTAINING TIOTROPIUM

RELATED APPLICATIONS

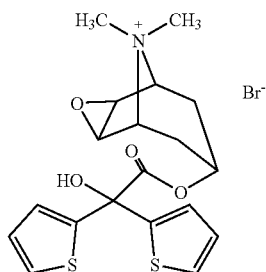
The present application is a continuation of U.S. Ser. No. 10/396,179 now U.S. Pat. No. 6,743,437 which is a continuation of U.S. Ser. No. 09/982,219, filed Oct. 17, 2001 now U.S. Pat. No. 6,537,568 which is a continuation of U.S. Ser. No. 09/587,485, filed Jun. 5, 2000 now U.S. Pat. No. 6,306,426 which is a continuation-in-part of U.S. Ser. No. 09/356,074 filed Jul. 16, 1999, now U.S. Pat. No. 6,110,485 which is a continuation of U.S. Ser. No. 09/150,990 filed Sep. 10, 1998, now abandoned which is a continuation of U.S. Ser. No. 08/908,094 filed Aug. 11, 1997, now abandoned.

FIELD OF THE INVENTION

The invention relates to powdered preparations containing tiotropium for inhalation, processes for preparing them as well as their use for preparing a pharmaceutical composition for treating respiratory complaints, particularly for treating COPD (chronic obstructive pulmonary disease) and asthma.

BACKGROUND OF THE INVENTION

Tiotropium bromide is known from European Patent Application EP 418 716 A1 and has the following chemical structure:



Tiotropium bromide is a highly effective anticholinergic with a long-lasting activity which can be used to treat respiratory complaints, particularly COPD (chronic obstructive pulmonary disease) and asthma. The term tiotropium refers to the free ammonium cation.

For treating the abovementioned complaints, it is useful to administer the active substance by inhalation. In addition to the administration of broncholytically active compounds in the form of metered aerosols and inhalable solutions, the use of inhalable powders containing active substance is of particular importance.

With active substances which have a particularly high efficacy, only small amounts of the active substance are needed per single dose to achieve the desired therapeutic effect. In such cases, the active substance has to be diluted with suitable excipients in order to prepare the inhalable powder. Because of the large amount of excipient, the properties of the inhalable powder are critically influenced by the choice of excipient. When choosing the excipient its particle size is particularly important. As a rule, the finer the excipient, the poorer its flow properties. However, good flow properties are a prerequisite for highly accurate metering when packing and dividing up the individual doses of preparation, e.g. when producing capsules (inhalettes) for powder inhalation or when the patient is metering the

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individual dose before using a multi-dose inhaler. Moreover, the particle size of the excipient is very important for the emptying characteristics of capsules when used in an inhaler. It has also been found that the particle size of the excipient has a considerable influence on the proportion of active substance in the inhalable powder which is delivered for inhalation. The term inhalable proportion of active substance refers to the particles of the inhalable powder which are conveyed deep into the branches of the lungs when inhaled with a breath. The particle size required for this is between 1 and 10 μm , preferably less than 6 μm .

The aim of the invention is to prepare an inhalable powder containing tiotropium which, while being accurately metered (in terms of the amount of active substance and powder mixture packed into each capsule by the manufacturer as well as the quantity of active substance released and delivered to the lungs from each capsule by the inhalation process) with only slight variations between batches, enables the active substance to be administered in a large inhalable proportion. A further aim of the present invention is to prepare an inhalable powder containing tiotropium which ensures good emptying characteristics of the capsules, whether it is administered to the patient using an inhaler, for example, as described in WO 94/28958, or in vitro using an impactor or impinger.

The fact that tiotropium, particularly tiotropium bromide, has a therapeutic efficacy even at very low doses imposes further conditions on an inhalable powder which is to be used with highly accurate metering. Because only a low concentration of the active substance is needed in the inhalable powder to achieve the therapeutic effect, a high degree of homogeneity of the powder mixture and only slight fluctuations in the dispersion characteristics from one batch of capsules to the next are essential. The homogeneity of the powder mixture and minor fluctuations in the dispersion properties are crucial in ensuring that the inhalable proportion of active substance is released reproducibly in constant amounts and with the lowest possible variability.

Accordingly, a further aim of the present invention is to prepare an inhalable powder containing tiotropium which is characterised by a high degree of homogeneity and uniformity of dispersion. The present invention also sets out to provide an inhalable powder which allows the inhalable proportion of active substance to be administered with the lowest possible variability.

DETAILED DESCRIPTION OF THE INVENTION

It was found that, surprisingly, the objective outlined above can be achieved by means of the powdered preparations for inhalation (inhalable powders) according to the invention described hereinafter.

Accordingly, the present invention relates to inhalable powders containing 0.04 to 0.8% of tiotropium mixed with a physiologically acceptable excipient, characterised in that the excipient consists of a mixture of coarser excipient with an average particle size of 15 to 80 μm and finer excipient with an average particle size of 1 to 9 μm , the proportion of finer excipient representing 1 to 20% of the total amount of excipient. Inhalable powders which contain 0.08 to 0.64%, most preferably 0.16 to 0.4% of tiotropium, are preferred according to the invention.

By tiotropium is meant the free ammonium cation. The counter-ion (anion) may be chloride, bromide, iodide, methanesulphonate, para-toluenesulphonate or methyl sulphate. Of these anions, the bromide is preferred.